Complete Summary

GUIDELINE TITLE

WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus.

BIBLIOGRAPHIC SOURCE(S)

World Health Organization (WHO). WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. Geneva, Switzerland: World Health Organization (WHO); 2006. Various p. [88 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Infection with avian influenza A (H5N1) virus

Note: The guidelines apply to the current situation in which no efficient or sustained human-to-human transmission of the virus is known to be occurring.

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Prevention

Risk Assessment
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To review and update recommendations on clinical case management of patients infected with the avian influenza A (H5N1) virus, as well as to review and update recommendations on the use of antiviral drugs as chemoprophylaxis

TARGET POPULATION

- Patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus in a non-pandemic situation (*for treatment*)
- Individuals at risk for H5N1 infection (*for chemoprophylaxis*), including the following groups:
    - Household or close family contacts of a strongly suspected or confirmed H5N1 patient (high risk)
    - Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal) if personal protective equipment may not have been used properly (medium risk)
    - Individuals with unprotected and very close direct exposure to sick or dead animals infected with the H5N1 virus or to particular birds that have been directly implicated in human cases (medium risk)
    - Health care personnel in close contact with strongly suspected or confirmed H5N1 patients without any or with insufficient personal protective equipment. This group also includes laboratory personnel who might have an unprotected exposure to virus-containing samples (medium risk)
    - Health care workers not in close contact (distance greater than 1 metre) with a strongly suspected or confirmed H5N1 patient and having no direct contact with infectious material from that patient (low risk)
    - Health care workers who used appropriate personal protective equipment during exposure to H5N1 patients (low risk)

- Personnel involved in culling non-infected or likely non-infected animal populations as a control measure (low risk)
- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal), who used proper personal protective equipment (low risk)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Discouragement of self-medication in the absence of appropriate clinical or public health advice
2. Treatment of patients with confirmed or strongly suspected human infection with the avian influenza A (H5N1) virus, where neuraminidase inhibitors are available for therapy:
    - Oseltamivir treatment
    - Zanamivir treatment
    - Neuraminidase inhibitor and an M2 inhibitor treatment
3. Treatment of patients with confirmed or strongly suspected H5N1 infection, where neuraminidase inhibitors are not available for therapy:
    - Amantadine or rimantadine as a first line treatment
4. Initiation of antiviral chemoprophylaxis based on risk stratification of patients
5. Antibiotics for prevention and treatment of severe community-acquired pneumonia
6. Other co-interventions (considered but not recommended):
    - Corticosteroids
    - Immunoglobulin and interferon
    - Ribavirin (specifically not recommended for pregnant women)

MAJOR OUTCOMES CONSIDERED

- Critical outcomes for treatment interventions:
    - Mortality
    - Duration of hospitalization
    - Incidence of lower respiratory tract complications
    - Antiviral drug resistance
    - Serious adverse effects
- Critical outcomes for chemoprophylaxis:
    - Outbreak control
    - Drug resistance
    - Serious adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Preparation of the Background Documentation

Background documentation was prepared in order to assist the World Health Organization (WHO) Rapid Advice Guidelines Group on Avian Influenza in its task of updating earlier guidance on the treatment and prophylaxis of avian influenza A (H5N1) infection in humans.

Summaries of the best available evidence were prepared to inform six primary questions regarding the treatment and prophylaxis of H5N1:

- Should oseltamivir be used for treatment or prophylaxis?
- Should zanamivir be used for treatment or prophylaxis?
- Should amantadine or rimantadine be used for treatment or prophylaxis?
- Should ribavirin be used for treatment?
- Should corticosteroids, immunoglobulin or interferon be used for treatment?
- Should broad spectrum antibiotics be used for the prevention of secondary pneumonia?

Additional questions included what the dose and length of treatment should be, particularly for oseltamivir, and what the mode of delivery should be, particularly for zanamivir.

Identification of Important Outcomes

A list of potential outcomes to be considered by the panel was initially developed by two reviewers. The team preparing the evidence summaries independently scored the relative importance of each outcome from 1 to 9, where 7 to 9 indicated the outcome was critical for a decision, 4 to 6 indicated it was important, and 1 to 3 indicated it was not important. Because the relative importance of some outcomes depended on whether a drug was being used for treatment or prophylaxis and whether there was human-to-human transmission, this was done for four scenarios. The individual scores were discussed and disagreements were resolved by consensus. Outcomes were included roughly in order of their relative importance in evidence tables; outcomes that were considered not important (a score of 3 or less) were not included.

A similar exercise was undertaken by the Guidelines Group prior to their meeting and the Cochrane Consumers network was consulted through their electronic discussion list. Both were asked to identify additional important outcomes not included in the list of potential outcomes identified by the team that prepared the background documentation.

Search Strategy

The search strategy aimed to identify systematic reviews, recent randomized trials (2005-6) for the treatment and prophylaxis of any influenza, and case series, animal studies, and in vitro studies for the treatment of H5N1.

For systematic reviews, the Cochrane Library (Issue 1, 2006) was searched for records with influenza in the title, and PubMed for records with influenza in the title using the research methodology filter for systematic reviews: (influenza) AND systematic [sb] Field: Title.

For randomized controlled trials PubMed was searched using the following search strategy: influenza Field: Title, Limits: Publication Date from 2005 to 2006, Randomized Controlled Trial (publication type).

In vitro and animal studies of the effectiveness of compounds against H5N1 virus were identified using PubMed searches. The terms "zanamivir or oseltamivir or amantadine or rimantadine or interferon or ribavirin" and "H5N1 or avian influenza" were used in each search. The term "in vitro" was added to the first search to identify in vitro studies and the limit "animal" was applied to the first search to identify studies of these treatments in animals. Published case-series of H5N1 infection in humans were identified with a search of PubMed using the terms "H5N1" and limited to case series and human studies. For case series data, articles with the most complete data were selected and no patients were duplicated. References of all papers were scanned for additional relevant studies. All searches were conducted between 17 and 21 February 2006.

Draft summaries of the evidence were sent to the members of the Guidelines Group prior to the meeting, and they were asked to identify any important evidence that had not been included. Drafts were also sent to four clinical experts for review and to identify any important evidence that was missing.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence

The evidence was assessed according to the methodology described by the GRADE working group. Briefly, in this system the quality of evidence is classified as "high", "moderate", "low", or "very low" based on methodological characteristics of the available evidence for a specific health care problem. The definition of each is provided below.

- **High**: Further research is very unlikely to change the confidence in the estimate of effect.
- **Moderate**: Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
- **Low**: Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
- **Very low**: Any estimate of effect is very uncertain.

Note: Factors that are considered in classifying evidence are: the study design and rigour of its execution, the consistency of results and how well the evidence can be directly applied to patients, interventions, outcomes and comparator. Other important factors are whether the data are sparse or imprecise and whether there is potential for reporting bias. For human patients with avian influenza A

(H5N1), there are currently no clinical trials in patients with the disease, which immediately raises uncertainty about whether the evidence that is available for seasonal influenza can be directly applied. It is important to note that a group of trials can be "high quality" evidence for one question, but because of uncertainty about their applicability or directness, can be "very low" quality evidence for a different question.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Selection Criteria, Data Collection, and Judgements

Systematic reviews were used to summarize the evidence from randomized trials for any influenza. Titles identified from the searches for reviews were assessed and the quality of relevant reviews was screened by two reviewers using a checklist. For each question data were extracted for all of the outcomes that were judged to be important, beginning with the most recent review of good quality, and supplementing that with additional data from other good quality reviews that addressed the same question.

Evidence profiles were created using the GRADE approach, using the GRADE profiler software (v1.12). Using this approach, assessments of the quality of evidence for each important outcome take into account the study design, limitations of the studies, consistency of the evidence across studies, the directness of the evidence, and the precision of the estimate. A liberal approach to assessment of study limitations was taken and the quality of evidence was not lowered because of reporting limitations, such as not clearly reporting whether there was concealment of allocation in trials. Three main criteria were used for assessing trial limitations: concealment of allocation, blinding and follow-up. If most of the evidence for an outcome (based on the weight given to each study in the meta-analysis) came from trials that did not have serious limitations, the overall assessment for that outcome was that there were no important limitations.

Because all of the evidence from trials was indirect for avian influenza A (H5N1), that is, it was for other influenza, there was major uncertainty about its applicability for H5N1, and this lowered the confidence in the estimates of effect for H5N1 for all of the important outcomes other than side effects, which could be expected to be the same. This does not mean that the trials were of low quality, but the quality of the evidence from (non H5N1 influenza) clinical trials is low for addressing questions about the management of H5N1 influenza.

For minor adverse effects occurring in the context of treatment there was also some uncertainty about the directness of the evidence because it was uncertain whether the outcomes reported were adverse effects or symptoms of influenza.

If data were available, estimates of the relative effect for continuous outcomes, such as duration of disease, were calculated by dividing the weighted mean difference (WMD) by the weighted average of the mean for the control group; using the percent of information that each mean difference contributed to the WMD as the weight. All estimates of effect size were expressed as relative risk if it

is possible to calculate it from the data provided, with absolute risk estimates included where appropriate.

One reviewer extracted data from the reviews and prepared drafts of the evidence profiles with detailed footnotes explaining the judgments that were made. These were checked by at least one other member of the team and discussed with the team that prepared the background documentation.

The quality of outcomes measured in each animal study was judged based on whether or not 1) pathogenicity of the virus was tested in the model, 2) statistical methods were adequate, and 3) a significant effect was demonstrated. The quality of measures used to determine inhibition of virus replication for each in vitro study was not evaluated.

Information on virus strain, compound, assay, comparisons, outcome of viral replication inhibition, outcome of neuraminidase inhibition and conclusions were extracted from each in vitro study. Information on virus strain, animal model, treatment, regimen, numbers in experimental and control group, outcome of survival, outcome of viral titer, outcome of resistance measurements and conclusion were extracted from each animal study. Information on treatment, dose, regimen, number treated and not treated, outcomes, place and year of case series, authors' remarks and conclusion was extracted from the human case series. A description of illness for each case-series was obtained from the review article by the Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. One person extracted these data and a second person verified the extracted data. Any inconsistencies were discussed and resolved by consensus. This information was used to supplement data from non-H5N1 clinical trials.

All of the evidence profiles and additional tables were sent to four external clinical experts and all of the members of the Guidelines Group for review prior to the meeting of the Guidelines Group.

Summary of Findings Tables

The key findings for each question for which non-H5N1 clinical trial evidence was available were summarized in tables, with the most important findings from the systematic reviews together with additional information specific to H5N1 from case reports, animal studies, and in-vitro studies.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The recommendations were drafted according to the GRADE method for assessing quality of evidence and strength of recommendations. A guideline panel comprising international scientists and experts in clinical treatment of avian and seasonal influenza, guideline methodology, basic research, policy making,

pharmacology and virology was convened in March 2006. The panel was asked to identify critical clinical outcomes for the purposes of making the recommendations. Mortality, duration of hospitalization, incidence of lower respiratory tract complications, resistance and serious adverse effects were rated as critical outcomes in the assessment of treatment interventions for human infection with avian influenza A (H5N1). For chemoprophylaxis, outbreak control, drug resistance and serious adverse effects were rated as critical outcomes. All outcomes reported in the clinical trials are summarized in the evidence profiles, set out in Annex 3 of the original guideline document.

The panel reviewed the evidence summaries and the draft guidelines and made recommendations. For all except one recommendation consensus was reached.

Formulation of the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs and values and preferences, described in the "Remarks" for each recommendation. "Values" are the desirability or preference that individuals exhibit for a particular health state. Individuals usually assign less value to and have less preference for more impaired health states (e.g., death or dependency after a stroke) compared to other health states (e.g., full health or having a very mild stroke without serious sequelae). In this document, the term "values" refers to the relative worth or importance of a health state or consequences (benefits, harms and costs) of a decision.

Very little information about costs of treatment or chemoprophylaxis was available to the panel, so for this guideline the main cost consideration was the acquisition cost of the antiviral drugs. Estimates of current acquisition costs are in Section 8 on drug supply in the original guideline document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendations are classified as "strong" or "weak" recommendations, as recommended in the GRADE methodology.

"Strong" recommendations can be interpreted as:

- Most individuals should receive the intervention.
- Most well informed individuals would want the recommended course of action and only a small proportion would not
- The recommendation could unequivocally be used for policy making.

"Weak" recommendations can be interpreted as:

- The majority of well informed individuals would want the suggested course of action, but an appreciable proportion would not
- Values and preferences vary widely
- Policy making will require extensive debates and involvement of many stakeholders

COST ANALYSIS

The guideline developers reviewed published cost analyses.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were revised by the World Health Organization (WHO) secretariat according to the recommendations from the panel and circulated to the panel members and other experts for peer review. Comments were reviewed by the Chair of the guidelines group and the WHO secretariat and were incorporated into the final version. A record of comments not included was kept and is available on request, with reasons for the rejections.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The rating schemes for the quality of the evidence (very low, low, moderate, high) and the strength of the recommendations (weak, strong) are defined at the end of the "Major Recommendations" field.

Recommendations

Self-medication in the absence of appropriate clinical or public health advice is discouraged.

Context: Treatment of patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus in a non-pandemic situation where neuraminidase inhibitors are available for therapy.

Rec 01: In patients with confirmed or strongly suspected H5N1 infection, clinicians should administer oseltamivir treatment as soon as possible (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance and costs of treatment. Despite the lack of controlled treatment data for H5N1, this is a strong recommendation, in part, because there is a lack of known effective alternative pharmacological interventions at this time. The recommendation applies to adults, including pregnant women and children. Until further information becomes available, the current treatment regimen for H5N1 is as recommended for early treatment of adults, special patient groups (e.g., those with renal insufficiency) and children with *seasonal* influenza.

Rec 02: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians might administer zanamivir (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on the prevention of death in an illness with high case fatality. It places a relatively low value on adverse effects (including bronchospasm), the potential development of resistance and costs of treatment. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir may be active against some strains of oseltamivir resistant H5N1 virus. The recommendation applies to adults, including pregnant women and children. Use of zanamivir requires that patients are able to use the Diskhaler device. Until further information becomes available, the current treatment regimen for (H5N1) infection is the same as recommended for early treatment of adults and children with seasonal influenza.

Although the quality of evidence when considered on a continuum is lower for the use of zanamivir compared to oseltamivir, the overall quality of evidence in the four category grading system is very low for both interventions.

Rec 03: If neuraminidase inhibitors <u>are available</u>, clinicians should <u>not</u> administer amantadine alone as a first-line treatment to patients with confirmed or strongly suspected human infection with avian influenza A (H5N1) (strong recommendation, very low quality evidence).

Remarks: Although recognizing that the illness is severe, this recommendation places a high value on the potential development of resistance and avoiding adverse effects. This is a strong recommendation in part, because of the availability of other options for treatment that may be more effective.

Rec 04: If neuraminidase inhibitors are <u>not available</u> and especially if the virus is known or likely to be susceptible, clinicians might administer amantadine as a first-line treatment to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places a relatively low value on adverse effects and the development of resistance in a situation without alternative pharmacological treatment. Until further information becomes available, the current treatment regimen for (H5N1) infection is the same as recommended for early treatment of adults and children with seasonal influenza. The use of amantadine should be guided by knowledge about local resistance patterns, and special consideration of the benefits and harms in patients at higher risk for adverse outcomes (e.g., pregnant patients).

Rec 05: If neuraminidase inhibitors are available, clinicians should not administer rimantadine alone as a first-line treatment to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (strong recommendation, very low quality evidence).

Remarks: Although recognizing that the illness is severe, this recommendation places a high value on the potential development of resistance and avoiding adverse effects. This is a strong recommendation in part because of the availability of other options for treatment that may be more effective.

Rec 06: If neuraminidase inhibitors are <u>not available</u> and especially if the virus is known or likely to be susceptible, clinicians might administer rimantadine as a first-line treatment to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places a relatively low value on adverse effects and the development of resistance. The use of rimantadine should be guided by knowledge about local antiviral resistance patterns, and special consideration of the benefits, harms, burdens and cost in patients at higher risk for adverse outcomes. Rimantadine has generally a more favorable side effect profile than amantadine.

Rec 07: If neuraminidase inhibitors are available and especially if the virus is known or likely to be susceptible, clinicians might administer a combination of neuraminidase inhibitor and M2 inhibitor to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (weak recommendation, very low quality evidence). This should only be done in the context of prospective data collection.

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places a relatively low value on adverse effects, the potential development of resistance and costs associated with therapy. The use of combination therapy should be guided by knowledge about local antiviral resistance patterns under special consideration for the benefits and downsides in patients of higher risk for adverse outcomes. Combination therapy should only be carried out if detailed and standardized clinical and virological data collection is in place at the start of therapy (prospective data collection). Clinicians should carefully determine which patients (e.g., severely ill patients) could receive combination therapy.

Chemoprophylaxis

Antiviral chemoprophylaxis should generally be considered according to the risk stratification described below. It is based on observational data for reported cases of human H5N1 infection and on high quality data from studies of seasonal influenza.

High risk exposure groups are currently defined as:

- Household or close family contacts[1] of a strongly suspected or confirmed H5N1 patient, because of potential exposure to a common environmental or poultry source as well as exposure to the index case.

Moderate risk exposure groups are currently defined as:

- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal) if personal protective equipment may not have been used properly.

- Individuals with unprotected and very close direct exposure[2] to sick or dead animals infected with the H5N1 virus or to particular birds that have been directly implicated in human cases.
- Health care personnel in close contact with strongly suspected or confirmed H5N1 patients, for example during intubation or performing tracheal suctioning, or delivering nebulised drugs, or handling inadequately screened/sealed body fluids without any or with insufficient personal protective equipment. This group also includes laboratory personnel who might have an unprotected exposure to virus-containing samples.[3]

[1] A close contact may be defined as an individual sharing a household with, or remaining unprotected whilst within speaking distance (<1 metre) of, or in the care of, a patient with confirmed or strongly suspected H5N1 infection.
[2] Examples of high risk exposure based on confirmed transmission to humans include: unprotected exposure to infected animal products such as consumption of blood from H5N1 infected ducks; preparation of food or other products from infected animals (e.g., plucking feathers); or prolonged exposure to infected birds in a confined space, such as playing with pets.
[3] This definition of moderate risk is based on very few cases recognized under these situations to date. As circumstances may change rapidly, it would be reasonable to consider the moderate and high-risk groups together for prophylaxis decisions. If a particular patient has been implicated in possible human-to-human transmission, then these examples of exposures could be defined as high risk.

Low risk exposure groups are currently defined as:

- Health care workers not in close contact (distance greater than 1 metre) with a strongly suspected or confirmed H5N1 patient and having no direct contact with infectious material from that patient.
- Health care workers who used appropriate personal protective equipment during exposure to H5N1 patients.
- Personnel involved in culling non-infected or likely non-infected animal populations as a control measure.
- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal), who used proper personal protective equipment.

In the present absence of sustained human-to-human transmission, the general population is not considered at risk.

Rec 08: In high-risk exposure groups oseltamivir should be administered as chemoprophylaxis continuing for 7-10 days after the last known exposure (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be used continuously for 7 to 10 days after last known exposure. Oseltamivir has been used for as long as 8 weeks for chemoprophylaxis of seasonal influenza. The dose of oseltamivir for H5N1 chemoprophylaxis should be that used in seasonal influenza. This recommendation also applies to pregnant women in the high risk exposure group.

Rec 09: In moderate risk exposure groups oseltamivir might be administered as chemoprophylaxis, continuing for 7-10 days after the last known exposure (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be used continuously for 7 to 10 days after last known exposure. Oseltamivir has been used for as long as 8 weeks for chemoprophylaxis of seasonal influenza. The dose of oseltamivir for H5N1 chemoprophylaxis should be that used in seasonal influenza. This recommendation applies to pregnant women in the moderate risk exposure group.

Rec 10: In low risk exposure groups oseltamivir should probably not be administered for chemoprophylaxis (weak recommendation, very low quality of evidence).

Remarks: This recommendation places a high value on avoiding adverse effects, potential development of resistance and cost. It places a lower value on preventing the low risk of H5N1 disease.

Rec 11: Pregnant women in the low exposure risk groups should not receive oseltamivir for chemoprophylaxis (strong recommendation, very low quality of evidence).

Remarks: This recommendation places a high value on avoiding possible but uncertain harm associated with oseltamivir chemoprophylaxis during pregnancy. It places a lower value on preventing the low risk of H5N1 disease.

Rec 12: In high risk exposure groups zanamivir should be administered as chemoprophylaxis, continuing for 7-10 days after the last known exposure (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be used continuously for 7 to 10 days after last known exposure. The dose of zanamivir should be that used for seasonal influenza chemoprophylaxis. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir may be active against some strains of oseltamivir-resistant H5N1 virus. Consequently, it might be a reasonable choice for health care workers with a high-risk exposure to an oseltamivir-treated H5N1 patient. This recommendation also applies to pregnant women who have high-risk exposure.

Rec 13: In moderate risk exposure groups, zanamivir might be administered as chemoprophylaxis, continuing for 7-10 days after the last known exposure (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and continued for 7 to 10 days after last known exposure. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir may be active against some

strains of oseltamivir resistant H5N1 virus. This recommendation also applies to pregnant women in the moderate risk exposure group.

Rec 14: In low risk exposure groups zanamivir should probably not be administered for chemoprophylaxis (weak recommendation, very low quality of evidence).

Remarks: This recommendation places a high value on avoiding adverse effects, possible development of resistance and cost. It places a lower value on preventing the low risk of H5N1 disease.

Rec 15: Pregnant women in the low risk exposure group should not receive zanamivir for chemoprophylaxis (strong recommendation, very low quality of evidence).

Remarks: This recommendation places a high value on avoiding possible but uncertain harm associated with zanamivir during pregnancy. It places a lower value on preventing the low risk of H5N1 disease.

Rec 16: If the virus is known or likely to be an M2 inhibitor resistant H5N1 virus, amantadine should not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on avoiding adverse effects in a situation when no drug efficacy would be expected.

Rec 17: If neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible, amantadine might be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in high or moderate risk exposure groups (weak recommendation, very low quality evidence).

Remarks: This recommendation does not apply to pregnant women, the elderly, people with impaired renal function and individuals receiving neuropsychiatric medication or with neuropsychiatric or seizure disorders. It places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known for 7-10 days after the last known exposure. Amantadine has been used for as long as 6 weeks for chemoprophylaxis of seasonal influenza A. This recommendation applies when neuraminidase inhibitors are not available or have limited availability.

Rec 18: If neuraminidase inhibitors are not available and even if the virus is known or likely to be susceptible, amantadine should probably not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in low risk exposure groups (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on avoiding adverse events, development of resistance, and cost. It places a lower value on preventing the low risk of H5N1 disease.

Rec 19: In pregnant women, the elderly, people with impaired renal function and individuals receiving neuropsychiatric medication or with neuropsychiatric or seizure disorders amantadine should not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality of evidence).

Rec 20: If the virus is known or likely to be M2 inhibitor resistant H5N1 virus, rimantadine should not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on avoiding adverse effects in a situation when no drug efficacy would be expected.

Rec 21: If neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible, rimantadine might be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in high or moderate risk exposure groups (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and continued for 7-10 days after the last known exposure. Rimantadine has been used for as long as 7 weeks for chemoprophylaxis of seasonal influenza A. This recommendation applies when neuraminidase inhibitors are not available or have limited availability. This recommendation does not apply to pregnant women.

Rec 22: If neuraminidase inhibitors are not available and even if the virus is known or likely to be susceptible, rimantadine should probably not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in low risk exposure groups (weak recommendation, very low quality evidence).

Remarks: This recommendation places a high value on avoiding adverse events, development of resistance, and cost. It places a lower value on preventing the low risk of H5N1 disease.

Rec 23: In pregnant women rimantadine should not be administered for chemoprophylaxis of human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality of evidence).

Rec 24: In patients with severe community acquired pneumonia regardless of the geographical location, clinicians should follow appropriate clinical practice guidelines (strong recommendation, the

panel has not judged the quality of the evidence for this recommendation).

Remarks: The choice of antibiotics should be based on knowledge of local pathogens, other co-morbidities and resistance patterns. Hospitals should have local antimicrobial surveillance data that can be used to inform the choice. Further advice about monitoring antimicrobial resistance is available in the World Health Organization (WHO) Global Strategy for Containment of Antimicrobial Resistance, at http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf. Local standard treatment guidelines should be updated regularly.

Rec 25: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus who do <u>not</u> need mechanical ventilation and have no other indication for antibiotics, clinicians should <u>not</u> administer prophylactic antibiotics (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: This is a strong recommendation in part because there is no evidence that antibiotic chemoprophylaxis reduces the risk of bacterial superinfection in H5N1 or seasonal influenza, whether or not the patients require mechanical ventilation. Antibiotics are likely to select for resistant bacteria, if superinfection occurs. Thus, at present there are no known clinical net benefits from chemoprophylaxis with antibiotics.

Rec 26: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus who need mechanical ventilation, clinicians should follow clinical practice guidelines for the prevention or treatment of ventilator associated or hospital acquired pneumonia (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: As the risk for bacterial infection in mechanically ventilated patients is increased, this recommendation places a high value on avoiding consequences of proven or suspected bacterial infection and a low value on adverse effects of antibiotics, the development of resistance, and cost. Appropriate broad spectrum antibiotic therapy should be instituted with a commitment to tailor antibiotics as soon as possible on the basis of serial clinical and anti-microbiologic data.

Rec 27: In pregnant patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should not administer ribavirin as treatment or chemoprophylaxis (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on avoiding the high risk of teratogenic effects of ribavirin during pregnancy.

<u>Definitions</u>:

Quality of Evidence

The evidence was assessed according to the methodology described in GRADE (GRADE Working Group 2003):

- **High**: Further research is very unlikely to change the confidence in the estimate of effect.
- **Moderate**: Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.
- **Low**: Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.
- **Very low**: Any estimate of effect is very uncertain.

Strength of the Recommendations

"Strong" recommendations can be interpreted as:

- Most individuals should receive the intervention
- Most well informed individuals would want the recommended course of action and only a small proportion would not
- Could unequivocally be used for policy making

"Weak" recommendations can be interpreted as:

- The majority of well informed individuals would want the suggested course of action, but an appreciable proportion would not
- Values and preferences vary widely

CLINICAL ALGORITHM(S)

An algorithm for management of humans infected with avian influenza A (H5N1) virus is provided in Annex 9 of the original guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate pharmacological management of patients infected or at risk for infection with avian influenza A (H5N1) virus

POTENTIAL HARMS

Adverse effects of antiviral treatment and chemoprophylaxis as well as development of drug resistance. Refer to the "Harms" sections of the original guideline document for specific details.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- All recommendations are specific to the current pre-pandemic situation. Recommendations were based on careful consideration of the benefits, harms, burdens and cost of interventions. Risk categorizations for exposure were developed to assist countries in prioritizing the use of antiviral drugs where their availability is limited. Overall, the quality of the underlying evidence for all recommendations was very low. No data from controlled clinical trials of avian influenza A (H5N1) infection are available. The existing evidence is based on small observational case series of H5N1 patients, results from in vitro and animal model studies of H5N1, or the extrapolation of data from high quality studies conducted to evaluate the treatment and chemoprophylaxis of normal, or "seasonal," influenza. These shortcomings highlight the need for further research. While the quality of the evidence for some of the critical outcomes was moderate or low, the overall quality of evidence on which to base a summary assessment was very low for all antiviral drugs. Differences exist in the quality of evidence for individual critical outcomes among the various antiviral drugs.
- This advice pertains only to H5N1 infections in the current pre-pandemic situation. Recommendations will be updated as new information becomes available, if there is evidence for sustained human-to-human transmission of H5N1, or if another novel avian influenza virus emerges. Whenever feasible, sequential clinical data collection and virological sampling (for analysis at World Health Organization [WHO]-designated laboratories) should be performed during treatment or should apparent failures of chemoprophylaxis occur.
- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
- The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.
- All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Adaptation or Localization of Guidelines

The ministry of health should take the lead in the process of adapting or localising these treatment guidelines if local versions are needed. Depending on when such a process takes place, the steps involved should include:

- Appointing a guideline committee comprising clinicians and methodologists
- Determining the scope of the guidelines
- Defining the clinical questions to be addressed
- Updating the evidence tables if necessary
- Reviewing the recommendations in the guidelines. The recommendations may need to be modified at a national level, depending on the local values, availability of drugs and costs
- Disseminating the guidelines, with a "use by" date
- Developing a method to obtain feedback and plans for review and update

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

World Health Organization (WHO). WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. Geneva, Switzerland: World Health Organization (WHO); 2006. Various p. [88 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006

GUIDELINE DEVELOPER(S)

World Health Organization - International Agency

SOURCE(S) OF FUNDING

World Health Organization (WHO)

GUIDELINE COMMITTEE

Guideline Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Dr Richard Bellamy, Department of Infection and Travel Medicine, James Cook University Hospital, Marton Road, Middlesborough TS 4 3BW, United Kingdom; Dr John Beigel, National Institute of Health Clinical Center, 6700B Rockledge, MSC 7609, Bethesda, MD, USA; Dr Tawee Chotpitayasunondh, Queen Sirikit National Institute of Child Health, MOPH, 420/8 Rajavithi Road, Payathai, Rajatevi, Bangkok 10400, Thailand; Professor Chris Del Mar, Dean, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland 4229, Australia; Professor Jeremy Farrar, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam; Professor Frederick G. Hayden, Internal Medicine & Pathology, Health Sciences Center University of Virginia, Charlottesville, USA; Dr Azim Nagjdaliyev, Children Clinical Hospital, Azerbaijan; Dr Bülent Özbay, Head of Pulmonary Department, Yuzuncu Yil University Van, Turkey; Associate Professor Holger Schünemann, Italian National Cancer Institute Regina Elena, Rome, Italy & University at Buffalo, Rome, Italy (Chair of Rapid Advice Guidelines Meeting); Dr Norio Sugaya, Department of Pediatrics, Keio University Faculty of Medicine, Keiyu Hospital, Minato-mirai, 3-7-3, Nishi-ku, Yokohama-shi, Kanagawa 220-0012, Japan; Dr Tim Uyeki, Medical Epidemiologist, Influenza Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, MS A-32, Centers for Disease Control and Prevention, Atlanta, GA, USA; Dr Tran Tinh Hien, Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam; Dr Yazdan Yazdanpanah, Infectious Diseases Physician, Department of Infectious Disease, Tourcoing Hospital, Lille Schoole of Medicine, Pavillon Trousseau 135 rue de Président Coty F-59200 Tourcoing, France

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Potential conflicts of interest of contributors (refers to the period 2002-2006).

In the absence of clear guidance in the World Health Organization (WHO) *Guidelines for Guidelines* the group discussed the potential conflicts of interest and took the following decisions:

1. The declared interests were professional, rather than personal and/or specific (i.e., no shares or personal funding from the companies).
2. The members' professional expertise generally outweighed the potential conflict of interest.
3. The interest was declared to the group and reported in the report.

No panel members were asked to withdraw from either voting or recommendation formulation. All other interests declared do not represent a personal specific interest in the medicines under review.

Beigel - investigator (through NIH) on trials with Roche and Biocrest, no personal funding

Del Mar - funding for trials in unrelated therapeutic area from other companies, not in the last 4 years

Hayden - received multiple research grants for trials of antivirals, vaccines from Roche, Abbots, Biocrest and Merck over the past 4 years, the last of these was in July 2005

Schünemann - received research grants and honoraria from Pfizer, Amgen, Roche and AstraZeneca for development or consulting regarding of quality of life instruments for chronic respiratory diseases, no personal funding (all funds were deposited into research accounts or received by research group)

Sugaya - has received travel grant from Roche to attend meeting on avian influenza; Yazdanpanah - investigator on trials with Tibotec Pharmaceutical, no personal funding, has received travel grants from GSK, Roche, Boehringer, BMS, Pfizer, Abbot, Gilead to attend scientific meetings.

The remaining members of the panel have no conflict of interest relevant to declare.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the World Health Organization Web site.

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on April 23, 2010.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Copyright/Permission Requests

Date Modified: 5/17/2010